Section II (Remarks)

By the present amendment, Claims 1-8, 10, 16-17 and 24-26 are pending and rejected.

Although not believed to be necessary to impart patentability, to facilitate allowance, Claims 17, 25, and 26 have been amended to remove the word "around", as suggested by the Examiner.

Claim 8 is an independent claim directed to a process for purifying 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914). The process involves first forming a VA-2914 isopropanol hemisolvate by dissolving VA-2914 in isopropanol under heat. The resulting solution is cooled to obtain crystalline VA-2914 isopropanol hemisolvate. The crystalline VA-2914 isopropanol hemisolvate is then isolated from the mother liquor, which separates the isopropanol hemisolvate from impurities that are soluble in isopropanol. Claims 1-7 depend, directly or indirectly, from Claim 8.

Claim 1 (which depends from Claim 8) specifies that the VA-2914 isopropanol hemisolvate crystals are formed by crystallizing VA-2914 in isopropanol, and adds the further steps of separating the VA-2914 isopropanol hemisolvate crystals and converting VA-2914 isopropanol hemisolvate into VA-2914.

Claim 2 (which depends from Claim 1) specifies that the formation of VA-2914 isopropanol hemisolvate crystals involves dissolving VA-2914 in isopropanol under heat, and subsequently cooling the resulting solution, optionally under stirring.

Claim 3 (which depends from Claim 2) specifies that the VA-2914 and isopropanol mixture is heated at a temperature between 75°C and the solvent reflux temperature until complete dissolution of VA-2914, and subsequently, the resulting solution of VA-2914 in isopropanol is allowed to cool at a temperature between 0°C and 30°C.

Claim 4 (which depends from Claim 1) specifies that the VA-2914 isopropanol hemisolvate crystals are separated by filtration.

Claim 5 (which depends from Claim 1) specifies that the conversion of VA-2914 isopropanol hemisolvate into VA-2914 is carried out by recrystallization in a solvent, and Claim 6 (which depends from Claim 5), specifies that the solvent is ethanol/water or ethyl ether.

Claim 7 (which depends from Claim 8) specifies the manner in which the VA-2914 compound is initially obtained. The compound is initially obtained by acid hydrolysis of compound 3,3-(1,2-ethanedioxy)-5α-hydroxy-11β-(4-N,N-dimethylaminophenyl)-17α-acetoxy-19-norpregna-9-ene-20-one [carbinol acetate].

Claims 16 and 17 (which both depend from Claim 1) specify that the VA-2914 is in the form of a white crystalline solid (Claim 16), and has a melting point of 189°C (Claim 17).

Claim 10 as amended is an independent claim directed to a process for obtaining 17α-acetoxy-11β-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914) isopropanol hemisolvate. The process involves dissolving VA-2914 in isopropanol under heat, allowing the resulting solution to cool to a temperature between 0°C and 30°C, and isolating the resulting VA-2914 isopropanol hemisolvate.

Claim 24 is an independent claim directed to isolated VA-2914, in the form of white crystals.

Claim 25 is an independent claim directed to isolated VA-2914, in the form of crystals with a melting point of 189°C.

Claim 26 is an independent claim directed to isolated VA-2914, in the form of white crystals with a melting point of 189°C.

Applicants reserve the right to pursue any cancelled claims in a continuation or divisional application.

Declaration by Dr. Antonio Lorente Bonde-Larsen

In order to appropriately address the issues raised by the Examiner, provided herein is a Declaration by Dr. Antonio Lorente Bonde-Larsen, Research and Development Manager of Ragactives (currently, "the Gadea Group," which includes Ragactives and Crystal Pharma), hereinafter referred to as "the Declaration."

As discussed in the Declaration [point 5 (page 3)], one of the purposes of the Declaration is to point out what levels of purity are required by the Pharmaceutical Industry in relation with the active pharmaceutical ingredients (APIs) obtained for commercial use, and the importance of the relative amount (and type) of each impurity present together with the API. Another purpose of the Declaration is to point out Dr. Lorente's experience in relation with additional purifications following the process described by the primary reference (Kim) cited in the obviousness rejection. Finally, another purpose of the Declaration is to discuss on the reliability of the differential scanning calorimetry (DSC) technique for measuring the melting point of a compound.

While the Declaration is being submitted after final rejection, there are appropriate reasons why the information in the Declaration is necessary, and why it was not earlier submitted.

Despite the existence of previously submitted arguments, and a previously-submitted Declaration, the Examiner has maintained her rejections. Applicant maintains that there is a significant, patentable difference in purity between the VA-9214 material produced by Kim and that produced by the instantly claimed processes. Although not previously argued in this much detail, part of the difference has to do with the guidance provided by the U.S. Food and Drug Administration, and its European counterpart, as to what types of impurities, and at what levels, are permissible in an approved pharmaceutical ingredient ("API").

Applicant believed that the previous arguments and previously-submitted Declaration were sufficient to overcome the previous rejections, and that the additional showing of the exact types and quantities of impurities in the material produced by the claimed processes, and those present in the process disclosed by Kim, would not be necessary. However, as a previous rejection was maintained, it is clear that this level of detail is necessary to make a sufficient showing to the Examiner that material of the claimed purity is patentably distinct over the lower purity material produced according to the teachings of the cited Kim reference. For at least these reasons, the Declaration and supporting documents are necessary, and were not earlier submitted. Entry of the Declaration and supporting documents into the record is respectfully requested.

Rejection of Claims 1-8, 10, 16-17, and 24-26 Under 35 U.S.C. 103(a) Over Kim in view of PCT WO 99/45022 by Cook et al.

Claims 1-8, 10, 16-17, and 24-26 were rejected under 35 U.S.C. 103 (a) over Kim in view of PCT WO 99/45022 by Cook et al. ("Cook"). The rejection is respectfully traversed.

In the last paragraph of Page 3, the Examiner has stated that "the only difference" between the claimed process and the process disclosed in the Kim reference is that the hemisolvate was formed by cooling versus evaporation of solvent." Since both cooling and evaporation of solvent are known to induce crystallization, the Examiner considers that it would have been obvious for the skilled person in the art to replace one method for another one.

Applicant respectfully disagrees. The difference is not necessarily in how the hemisolvate is *formed*, but rather, in how the hemisolvate is *isolated*, namely in that according to the instant patent application the hemisolvate is isolated from impurities that remain in the solvent, rather than evaporating the solvent and retaining the impurities.

Isolation of the hemisolvate from the solvent increases the purity of the final product, by leaving isopropanol-soluble impurities in the solvent. In contrast, evaporation of the solvent (as done by Kim) leaves isopropanol-soluble impurities in the product.

For this reason alone, the obviousness rejection should be withdrawn.

The Articulated Basis for the Obviousness Rejections

The Examiner has not recognized the advantages of the purification process of the instant invention, and has stated her belief that:

a) a purity of 99.2% is not considered significantly different from that of 98.57%;

b) a melting point of "around" 189°C would fall within the range of 183-185°C taught by Cook; and

c) because VA-2914 has a medical use, it would have been obvious to further purify it.

A purity of 99.2% is significantly different from that of 98.57%

In point 6 (pages 3-8) of the Declaration, Dr. Lorente thoroughly discusses the statement of the Examiner that "(a) a purity of 99.2% is not considered significantly different from that of 98.57%". Firstly, Dr. Lorente provided comments regarding the quality level required by the Pharmaceutical Industry in relation with the active pharmaceutical ingredients ("APIs") obtained for commercial use and the importance of the relative amount of each impurity present together with the API [point 6, paragraphs A-H, pages 3-5]. Secondly, Dr. Lorente discussed and compared the results obtained after purifying VA-2914 according to Kim and according to the process claimed in this application [point 6, paragraphs I-K, pagers 5-7]. Finally, Dr. Lorente concluded that the quality of the purified product (VA-2914) following the process disclosed in the instant patent application, or following the process disclosed by Kim, is very different in view of the pharmaceutical requirements [point 6, paragraph L, page 8].

The analysis of VA-2914 obtained according to Kim, having a total purity of 98.57%, shows the presence of five impurities in an amount of more than 0.05% each, with the most significant impurities being [point 6, paragraphs I-J, pages 5-7]:

i) 17-α-hydroxy-17β-acetyl-11β-((N,N'-dimethyl-4'-amino)phenyl)-19-norandrosta-4,9-diene-3-one, hereinafter referred to as "compound (1)", in an amount of 0.16%, which must be reduced to less than 0.15% (according to ICH Q3A guidance);

ii) 17-α-acetoxy-17β-acetyl-11β-((N-methyl-4'-amino)phenyl)-19-norandrosta-4,9-diene-3-one, hereinafter referred to as compound (2)", in an amount of 0.97%, which corresponds with the metabolite of VA-2914 and can be present at levels of more than 0.15%, although a lower amount of this impurity would be desirable;

iii) p-bromo-dimethylaniline, hereinafter referred to as "compound (6)", in an amount of 0.11%, which corresponds with a compound which is a potentially genotoxic impurity, and, consequently, its amount level must be of less than 0.015%; in addition, this impurity is very different structurally from VA-2914 and, therefore, this kind of impurity should be avoided; and

iv) other impurities in minor amounts.

Consequently, the VA-2914 compound purified according to the process disclosed by Kim (purity 98.57%) does not have the quality needed for use as an API, and it is not acceptable for commercial purposes [the Declaration, point 6, paragraph L, page 8].

However, the claimed process allows one to obtain VA-2914 having a total purity of 99.20%. The analysis of this product shows the presence of only one impurity in an amount of more than 0.05%, namely the VA-2914 metabolite [compound (2)], in an amount of 0.69%. This amount is significantly lower than the amount of this impurity obtained following the process disclosed by Kim (0.97%). This impurity is present in an acceptable level, together with other impurities in amounts lower than 0.05%. As discussed in the Declaration, it is not necessary to identify impurities in amounts lower than 0.05%. (The Declaration, point 6, paragraph K, page 7].

Surprisingly, and advantageously, the potentially genotoxic impurity p-bromo-dimethylaniline, identified in the VA-2914 compound obtained according to Kim, is not present in the VA-2914 compound obtained according to the claimed process. This impurity (an aniline derivative), as discussed below, has been related with the presence of color in the final product.

Therefore, the quality of the VA-2914 compound obtained according to the claimed process fulfills all the requirements of EMEA and FDA guidance, and it is commercially acceptable [The Declaration, point 6, paragraph L].

Thus, in view of the amount and nature of the impurities which are present together with both the VA-2914 compound obtained according to Kim and the VA-2914 obtained according to the claimed invention, as well as the significance and relevance of these impurities, the statement by the Examiner that "a purity of 99.2% is not considered significantly different from that of 98.57%" is factually incorrect.

The Use of the Word "Around" to Define the Melting Point

To facilitate prosecution, the word "around" has been removed from each of the claims where it appeared, namely, Claims 17, 25 and 26. Thus, these claims are believed to distinguish over the cited references.

However, Applicants state for the record that it should be clear that in the context of melting points, "around" 189 would normally be construed as being higher than the range of 183-185°C taught by Cook, and, therefore that the claims as previously pending were patentably distinct over Cook.

Dr. Lorente, in point 8 (page 10) of his Declaration, states that the differential scanning calorimetry (DSC) technique for measuring the melting point of a compound is a fully reliable technique, and that it is possible to differentiate, without any doubt, between melting points of 183-185°C (mentioned for the product obtained according to Cook) and the melting point of 189°C (obtained for the product (VA-2914) purified according to the instantly claimed process in Claim 17, and as claimed in product claims 25 and 26).

Further, Dr. Lorente states that since the melting point is an indicative key to measure the purity of a compound, when the melting point is higher, the purity also increases. Color-free crystals (i.e., white crystals) are indicative of purity, and it is a very simple matter to obtain the melting point and to prove the purity of the compound [The Declaration, point 8, paragraph D, page 10].

It Would Not Have been Obvious to Further Purify Kim's Compound

The Examiner stated that "because VA-2914 has a medical use, it would have been obvious to further purify it." Applicant respectfully disagrees.

Dr. Lorente, based on his experience in relation with additional purifications following the process disclosed by Kim, in point 7 of his Declaration (page 9) states that the VA-2914 sample having a purity of 98.57% (obtained according to the process disclosed by Kim), once recrystallized and isolated from diethyl ether, cannot be re-dissolved again in that solvent in order to further purify the material using a solution-precipitation approach. In his opinion, the only possibility to purify it again in diethyl ether as solvent is by re-suspension, and, under those conditions, the quality of the VA-2914 compound obtained would be almost the same. Further, when a further recrystallization using another solvent (e.g., ethanol or ethanol/water) is performed, the impurity profile is similar, and the colored impurities, which correspond to the potentially genotoxic p-bromo-dimethylaniline, remain in the final VA-2914 product [The Declaration, point 7, paragraphs A-C, page 9].

For at least these reasons, it would not have been obvious to arrive at Applicant's purification method.

The Declaration further states that the white crystals obtained by the claimed purification process (by means of the hemisolvate obtained in the recrystallization with isopropanol followed by a filtration step) are related to the loss of the impurities associated with aniline derivatives, as for example, p-bromo-dimethylaniline.

The presence of white, color-free crystals is indicative of high purity. Given that p-bromo-dimethylaniline, a colored impurity, was identified in the process disclosed by Kim, the white, crystalline material obtained using the claimed processes is essentially free of dimethyl aniline derivatives such as p-bromo-dimethylaniline. As anilines are a group of compounds used as colorants or pigments in the industry, the presence of a colored VA-2914 product (such as the product produced according to the teachings of Kim) is indicative of the presence of a potentially genotoxic aniline derivative.

It Would Not Have Been Obvious to Use Chromatography to Purify VA-2914

In the context of the product claims, the Examiner states (page 5, last paragraph of the Office Action), that since it was known in the art that VA-2914 had a medicinal use, one of ordinary skill in the art would be motivated to improve the purity of the compound to reduce any adverse effect(s) due to impurity. The purportedly obvious purification method was chromatography, since Cook purportedly purified compounds of the type disclosed by Kim. The Examiner stated that it would have been *prima facie* obvious to use the purification process taught by Cook to obtain the compound of Kim in >99% purity.

Those of skill in the pharmaceutical arts would not look to chromatographic purification techniques, which are unsuitable for producing a compound at an industrial scale, as a way to purify pharmaceutical compounds like VA-2914. That is, it stands to reason that if one were seeking to produce a pharmaceutical compound at a commercial scale, one would not seek to use a purification method that is not readily applicable to commercial scale.

Further, the Examiner has made assumptions about the degree of purification afforded by Cook's chromatography. When Cook chromatographically separated crude products, he more often than not produced products with a purity significantly lower than 99%. Cook used chromatographic separation to purify a number of compounds throughout the working examples, but only claims to have isolated one intermediate in >99 % purity using chromatography (the last compound in Example 2). In most cases, the purity is not mentioned at all, in many cases, throughout Example 1, compounds are referred to as epimeric or isomeric mixtures. In one case, a compound (A-13) referred to as having "high purity" only had a purity of 84.7%.

Later on, in Example 4, Cook teaches that less pure fractions from initial column chromatography were further purified by flash SiO_2 column chromatography to afford a pure product, which was then recrystallized to give a crystalline product (>99% pure by HPLC). That is, even after initial column chromatography, and a further purification by flash chromatography, the material had to be recrystallized to obtain >99% purity.

Thus, Cook provides no likelihood of success that chromatographic separation would purify Kim's compounds to the degree obtained using the instantly claimed purification processes. Further, those of skill in the art would not look to chromatographic separation to produce commercial scale pharmaceutical compounds.

Accordingly, for at least the reasons stated herein, there are significant differences in purity between the products produced according to the claimed invention, and those produced in the cited references. The claimed purification processes, as well as the products produced using these processes, are patentably distinct from the products produced by, and processes disclosed by, Kim and Cook.

For any of the above reasons, Applicants respectfully request that the Examiner withdraw the rejections of Claims 1-8, 10, 16-17 and 24-26 under 35 U.S.C. 103 (a).

CONCLUSION

In light of the arguments presented above, it is requested that the rejection of the pending claims be withdrawn, and that the patentability of the pending claims likewise be acknowledged. All of Applicants' pending claims are now patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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